REMARKS

Applicants have amended claim 14 to more particularly point out and distinctly claim the subject matter which they regard as their invention. This amendment necessitates the amendments to claims 17 and 21. Applicants have also cancelled claims 1-13 and withdrawn claims 23-30. No new matter has been introduced by the above amendments.

Upon entry of the above amendments, claims 14-22 will be under examination. Reconsideration of the application, as amended, is requested in view of the remarks below.

Rejection under 35 U.S.C. § 112, 2nd paragraph

Claims 14-20 and 22[1] are rejected as being indefinite on two grounds. See the Office Action, page 3, lines 1-7. Applicants traverse each ground below:

(1) The Examiner points out that "[i]n claim 14 mention is made of 'linked to B' however no 'B' variable is present in the structure shown in the claim. Perhaps 'C' was really intended." See the Office Action, page 3, lines 4-5. Applicants agree and have replaced the character "B" recited in claim 14 with "C."

(2) The Examiner states that "[t]he proviso appearing in the $R^{a'}$ definition [recited in claim 14] lacks antecedent basis as the superscripts R^{d} and $R^{d'}$ do not appear in the R^{3} definition several lines above." See the Office Action, page 3, lines 6-7. Applicants acknowledge this deficiency and have removed this proviso from claim 14.

For the reasons set forth above, Applicants submit that claims 14-20 and 22 are no longer indefinite and request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 112, 1st paragraph

Claims 14-20 and 22 are rejected as failing to comply with the enablement requirement. See the Office Action, page 3, lines 8-9.

I

To support this rejection, the Examiner relies on relevant factors set forth in *In re Wands* 8 USPQ2d 1400 (CAFC, 1988), including: breadth of the claims, level of unpredictability in the

[1] In the Office Action, the Examiner rejects claim 23 as being indefinite. It appears that claim 23 should read "claim 22" since the Examiner has withdrawn claim 23 on the ground that it covers non-elected species.

art, guidance of the specification, state of the art, and working examples. See the Office Action, pages 4-5. Applicants respectfully traverse the Examiner's reliance on each of the factors below. Claim 14, the only independent claim, will be discussed first.

Breadth of the claims

The Examiner contends that "[s]pecification is not adequately enabled for the scope of piperazinediones claimed which can carry a variety of functional groups at R^a, R^b, $R^{a'}$, and $R^{b'}$ including nonlimiting scope of heterocycloalkyls and heteroaryls, both directly or indirectly attached to the piperazine ring. Additionally these rings can be further substituted with a list of substituents that in turn can contain more hetero rings or acyls of nonlimiting scope or any carboxylate ester groups. The same applies for the scope of alkyl, cycloalkyl, aryl, and arylalkoxy moieties wherever they appear such as in R1/R2/R3 definitions or Ra/Rb/Rb'/Re/Rf/Rg which can carry the same scope of substituents from a reading of the specification on p. 3. ... the claims cover compounds easily in the millions ... ." See the Office Action, page 3, line 12 to page 4, line 9.

Applicants have limited $R^{a'}$ recited in claim 14 to a single group, i.e., benzo[1,3]dioxol-5-yl, thereby significantly reducing the number of compounds covered by this claim.

Applicants would like to point out that the specification can enable a claim even though the claim covers a large number of compounds. Indeed, according to MPEP 2164.01,

> "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. ... As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. ..."

The instant specification already provides general guidance on how to prepare piperazinedione compounds. See page 7, line 19 to page 8, line 9. This general guidance can be used to prepare all piperazinedione compounds of amended claim 14. It also provides detailed description on preparing 35 specific piperazinedione compounds. See Examples 1-35. Further, the specification teaches in general how to administer a piperazinedione compound through various routes to a subject for treating an angiogenesis-related disorder. See page 10, line 1 to

page 11, line 13. This teaching can be applied to all of the piperazinedione compounds of amended claim 14. It also provides two *in vitro* assays for testing the efficacy of 26 piperazinedione compounds and an *in vivo* assay for confirmation of the efficacy of 6 of the 26 compounds. See Examples 36-38. Thus, in view of the specification, one skilled in the art would know, without undue experimentation, how to prepare all piperazinedione compounds covered by amended claim 14, how to determine which piperazinedione compounds of amended claim 14 are effective, and how to use the effective compounds to treat an angiogenesis-related disorder. Since the specification discloses at least one method of making and using the piperazinedione compounds that bear a reasonable correlation to the entire scope of amended claim 14, the enablement requirement is believed to have been satisfied even though amended claim 14 covers a large number of compounds.

Level of unpredictability in the art

The Examiner states that "the invention is pharmaceutical in nature as it involves inhibition of angiogenesis-a complicated biological process which involves dealing/interfering with the presence of angiogenic activators such as VEGF, basic fibroblast growth factor and inhibitors such as thrombospondin, angiostatin in order to be successful in reaching the primary and metastatic site of a tumor. It is well established that 'the scope of enablement varies inversely with the degree of unpredictability of the factors involved' and physiological activity is generally considered to be unpredictable." See the Office Action, page 4, lines 10-17.

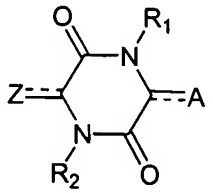
The Examiner appears to assert that claim 14 covers a large number of compounds, while the specification only discloses biological tests on a limited number of compounds for treating angiogenesis-mediated diseases. As mentioned above, the specification already provides biological tests on as many as 26 claimed compounds. Further, it is not necessary to test each compound of claim 14 for treating an angiogenesis-mediated disease. The law does not impose such a formidable burden on inventors seeking patent protection. "Appellants (here, Applicants) are **not** required to disclose every species encompassed by their claims even in an **unpredictable** art" (emphases added). *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). Such a holding is only reasonable, since it is very difficult, if not impossible, to test and disclose all operative species in the chemical and biotechnology fields. As pointed out by the *Angstadt* court

"[w]ithout undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do no cover them." *Id*, at 219. Indeed, narrowing the scope of claim 14 is unreasonable as it would lead to a grossly unjust result: other persons of ordinary skill in the art can easily avoid the claimed invention by conveniently selecting and using a untested embodiment, without undue experimentation.

Guidance of the specification

The Examiner asserts that "the compounds made and indicated as tested not representative of the instant scope but are closer to each other than to the remaining scope ...." See the Office Action, page 4, line 18 to page 5, line 1. Applicants disagree.

Amended claim 14 covers piperazinedione compounds of the following formula:



When ---- and ---- are double bonds, each of R_1 and R_2, independently, is H or $C(O)R^g$; A is $C(R^{a'}R^{b'})$; and Z is R_3O-(Ar)- $C(R^e)$, in which R_3 is C_1-C_6 alkyl substituted with aryl, $C(O)R^f$, or $S(O)R^f$; $R^{a'}$ is benzo[1,3]dioxol-5-yl; and $R^{b'}$ is H, C_1-C_6 alkyl, or aryl. Take compound 23 as an example. In compound 23, each of R_1 and R_2 is H; R_3 is C_1-C_6 alkyl substituted with aryl; $R^{a'}$ is benzo[1,3]dioxol-5-yl; and $R^{b'}$ is H. In other words, each group in compound 23 that corresponds to R_1, R_2, R_3, $R^{a'}$, and $R^{b'}$ is selected from no more than three alternative groups. Thus, contrary to the Examiner's assertion, compound 23 is representative of the scope of amended claim 14.

Further, as discussed above, the specification already provides general guidance on how to prepare and use all of the piperazinedione compounds of amended claim 14. Thus, even if the specific compounds disclosed in the specification are closer to each other than to other compounds of amended claim 14, the specification still provides adequate enablement to amended claim 14.

State of the art

The Examiner states that "[t]he compounds are piperazinedione derivatives substituted at the 3- and 5- positions with one of these requiring a very specific pattern -see R_3O-Ar-C(R^e)- requirement- while the other end can vary from H, alkyl, to having carbocyclic and hetero rings of non-limiting scope. While such compounds are known as evident from the art applied below, they are directed to only a small part of applicants' scope and thus do not evidence the many structural permutations permitted in the instant scope are known in the art for the same activity relied on herein." See the Office Action, page 5, lines 6-13.

Applicants would like to bring to the Examiner's attention that when variable Z recited in amended claim 14 is R_3O-Ar-C(R^e), variable A at the other end of the piperazine ring must be C($R^{a'}R^{b'}$), in which $R^{a'}$ is limited to benzo[1,3]dioxol-5-yl and $R^{b'}$ is limited to H, C_1-C_6 alkyl, or aryl. In other words, variable A recited in amended claim 14 does not have a non-limited scope as alleged by the Examiner. Further, given that $R^{a'}$ is limited to benzo[1,3]dioxol-5-yl, there is no structural permutation for this variable. Finally, as discussed above, compound 23 disclosed in the specification is representative of the scope of amended claim 14. Thus, in view of compound 23, one skilled in the art would know that other compounds of amended claim 14 would have similar activity as that of compound 23.

Working examples

The Examiner contends that "[t]he test data presented in examples 36-38 is scant as no actual data is reported only wording such as large number showed inhibition of HUVEC proliferation in eg. 36 or most inhibited VEGF inhibition in eg. 37 and out of 6 compounds tested in eg. 38, 4 showed ID50 values less than 3 mg/kg in mice and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree." See the Office Action, page 5, lines 14-19.

Applicants would like to point out that, to satisfy the enablement requirement, the specification is not required to provide a "clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree." Indeed, according to MPEP 2164.04,

> "[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, 1st paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enablement support.

As discussed above, one skilled in the art, in view of the specification, would know how to make and use all of the compounds of amended claim 14 without undue experimentation. Although Examples 36-37 of the Specification do not provide data on the compounds tested in the *in vitro* assays described therein, there is no reason to doubt the truth of the statements in these two Examples that "a large number of the [test compounds] inhibited HUVEC's proliferation" and that "most of [test] compounds inhibited tube formation induced by VEGF and some exerted complete inhibition." Thus, the disclosure in the specification must be taken as being in compliance with the enablement requirement.

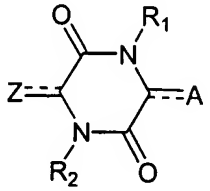
II

For the reasons set forth above, Applicants submit that amended claim 14 is enabled by the specification. So are claims 14-20 and 22, all of which depend from claim 14.

Rejection under 35 U.S.C. § 102(b)

Claims 14-22 are rejected as being anticipated by Teng et al, WO 01/95858 ("Teng"). See the Office Action, page 6, lines 7-8.

Independent claim 14 is discussed first. Claim 14, as amended, covers piperazinedione compounds of the following formula:



In this formula, A is H or $CH(R^aR^b)$ when ---- is a single bond, or $C(R^{a'}R^{b'})$ when ---- is a double bond; and $R^{a'}$ is **benzo[1,3]dioxol-5-yl**.

The Examiner states that Teng "describes many compounds within the instant scope for use as antitumor agents. See species appearing on p. 4 which includes a species (2nd one) within

claim 21." See the Office Action, page 6, lines 9-12. Teng lists seven piperazinedione compounds on page 4. However, in all of the seven compounds, the group corresponding to $R^{a'}$ recited in amended claim 14 is phenyl, 4-hydroxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-benzyloxyphenyl, thienyl, or 4-benzyloxypyridyl, not **benzo[1,3]dioxol-5-yl**. Thus, amended claim 14 is not anticipated by Teng. Neither are claims 15-22, all of which depend from claim 14.

Rejection under 35 U.S.C. § 103(a)

Claim 22 is rejected as being obvious over Teng. See the Office Action, page 6, lines 20-21.

Claim 22, similar to amended claim 14 from which it depends, covers piperazinedione compounds of the above formula, in which A is H or $CH(R^aR^b)$ when ---- is a single bond, or $C(R^{a'}R^{b'})$ when ---- is a double bond; and $R^{a'}$ is **benzo[1,3]dioxol-5-yl**.

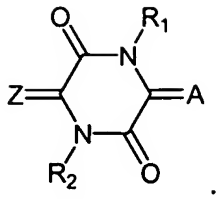
As mentioned above, Teng discloses seven compounds on page 4 and, in all of the seven piperazinedione compounds, the group corresponding to $R^{a'}$ is phenyl, 4-hydroxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-benzyloxyphenyl, thienyl, or 4-benzyloxypyridyl. Teng does not disclose or suggest piperazinedione compounds in which the group corresponding to $R^{a'}$ is **benzo[1,3]dioxol-5-yl**, as required by claim 22. Thus, claim 22 is not obvious over Teng.

Double patenting rejection

Claims 14-21 are rejected under the judicially created doctrine of obviousness-type double patenting on the ground that they are unpatentable over claims of U.S. Patent 6,635,649 ("the '649 patent"). See the Office Action, page 8, lines 19-20.

As discussed above, amended claim 14 covers piperazinedione compounds of the above formula, in which A is H or $CH(R^aR^b)$ when ---- is a single bond, or $C(R^{a'}R^{b'})$ when ---- is a double bond; and $R^{a'}$ is **benzo[1,3]dioxol-5-yl**.

The '649 patent was issued with 23 claims. Among them, claims 1-16 are compound claims and claims 17-23 are method claims. Claim 1 of the '649 patent, the broadest compound claim, covers piperazinedione compounds of the following formula:



In this formula, A is $C(R^aR^b)$, one of R^a and R^b is thienyl, furyl, pyridinyl, indolyl, 2-oxo-indolyl, aryl, alkyl, or alkyl substituted with aryl, and the other of R^a and R^b is H, alkyl, or aryl; in which alkyl and aryl are unsubstituted or substituted with one or more substitutents selected from the group consisting of halogen, hydroxyl, amino, alkylamino, arylamino, dialkylamino, diarylamino, cyano, nitro, mercapto, carbamido, carbamoyl, carboxyl, thioureido, thiocyanato, sulfonamido, C_1~C_6 alkyl, C_2~C_6 alkenyl, C_1~C_6 alkoxy, and aryl. Claim 17 of the '649 patent covers methods of treating tumor with piperazinedione compounds of a formula have the same scope of that recited in claim 1. Claims 1 and 17 of the '649 patent, as well as the claims dependent therefrom, do not disclose or suggest that either of R^a and R^b, which corresponds to $R^{a'}$, is **benzo[1,3]dioxol-5-yl**, as required by amended claim 14. Thus, amended claim 14 is not obvious over claims 1-23 of the '649 patent. Neither are claims 15-21, all of which depend from claim 14.

CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that claims 14-22, as pending, define subject matter that is definite, enabled, novel, and nonobvious. On this basis, it is submitted that these claims are now in condition for allowance, an action of which is requested.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges to deposit account 06-1050, referring to Attorney's Docket No. 16127-002003.

Respectfully submitted,

Date: 9-22-06

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